[19]中华人民共和国专利局

[11] 公开号 CN 1113234A

[12] 发明专利申请公开说明书

[21]申请号 94114311.2

[51]Int.Cl[6]
C07D233/54

[43]公开日 1995年12月13日

[22]申请日 94.12.29

[71]申请人 中国科学院上海有机化学研究所
地址 200032上海市枫林路354号
共同申请人 常州第三制药厂
[72]发明人 吴国生 周文娟 陈国平 金雄民
钱淑芹 陈荣清 王淑芬

[74]专利代理机构 江苏省专利事务所
代理人 徐冬涛 邵元领

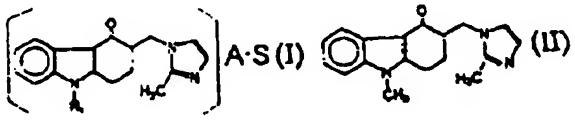
说明书页数: 附图页数:

[54]发明名称 恩丹西酮及其生理盐的合成

[57]摘要

本项发明涉及制备化学结构式（I）的化合物及其相应的游离碱（II）的方法。

结构式中：A表示盐酸、硫酸、氢溴酸、草酸、马来酸、高氯酸，可以和（II）生成合格生理盐的无机和有机酸；S表示为水的溶剂。

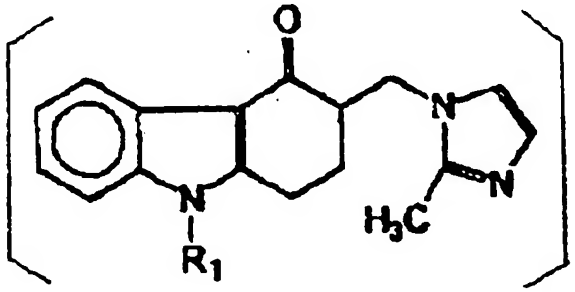


化合物（I）的化学名是1，1，2，2，3-五氢-9-甲基-3-[（2-甲基-咪唑-1-基）甲基]-4-氧代咔唑的生理盐的溶剂化物，是有效的5-HT_3，受体拮抗剂，临床上对由顺铂、非顺铂化疗和放疗引起的恶心、呕吐具有强疗效。

(BJ)第1456号

权 利 要 求 书

1．通式（Ⅰ）的制备方法：

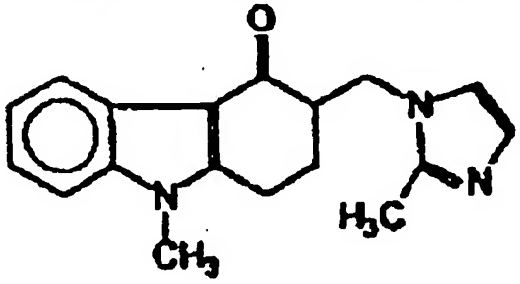


A·S(I)

结构式中：A表示盐酸、硫酸、氢溴酸、草酸、马来酸、有机酸或无机酸；S表示水溶剂；R_1表示 $C_1 \sim C_6$的直链或脂环状烷基；

通式（Ⅰ）的制备方法包括：

（A）通式（Ⅱ）的化合物或其被保护的衍生物或含量高于30%的反应混合物与A之间的固一液界面成盐反应；

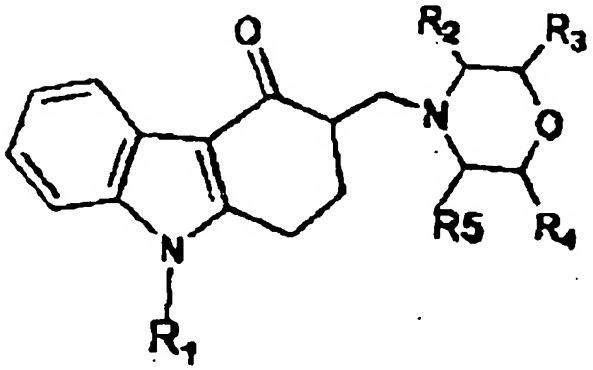


(II)

（B）通式（Ⅱ）的化合物或其被保护的衍生物或含量高于30%的反应混合物与A之间的液一气界面成盐反应。

2．根据权利要求1所述的通式（Ⅱ）的制备方法：

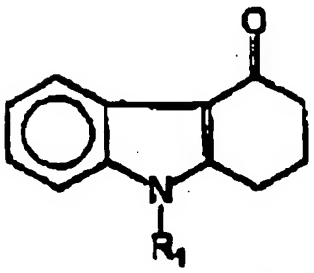
（C）通式（Ⅲ）的化合物和2—甲基咪唑或其他胺交换反应；



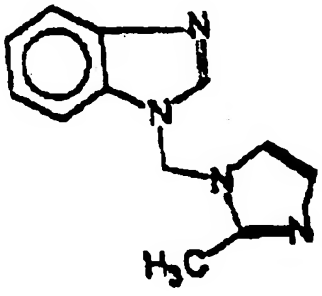
(III)

结构式中：R_1表示$C_1 \sim C_6$的直链或脂环状烷基，R_2、R_3、R_4、R_5表示$C_1 \sim C_3$短链正烷基或异烷基或氢原子，R_2、R_3、R_4、R_5可以是相同或不相同的取代基，或无取代基；

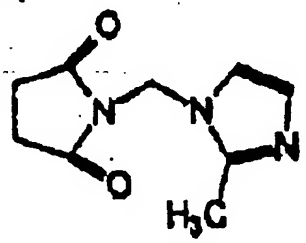
（D）化学结构式（IV）化合物和化学结构式（V）或（VI）化合物的酮交换反应；



(IV)



(VI)



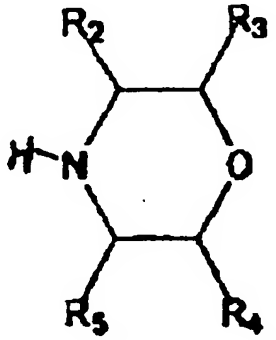
(V)

结构式中：R_1表示$C_1 \sim C_6$的直链或脂环烷基；

（E）化学结构式（IV）化合物，多聚甲醛和2—甲基咪唑的催化缩合反应，反应中所用的固体催化剂是$AgNO_3$、$Cu_2X_2(X=Cl,Br,I)$、$Cu(OAc)_2$、Al_2O_3 Lewis酸或它们的混合式复合催化剂.

3．根据权利要求2所述的制备化学结构式（III）的方法其中包括：

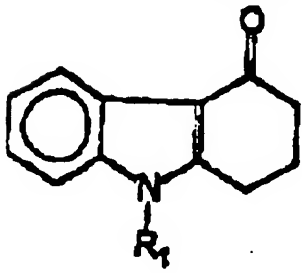
（F）化学结构式（IV）化合物，多聚甲醛和结构式（VII）化合物的催化缩合反应，反应中所用的固体催化剂是$AgNO_3$、$Cu_2X_2(X=Cl,Br,I)$、$Cu(OAc)_2$、Al_2O_3 Lewis酸或它们的混合式复合催化剂或盐酸、硫酸、无机酸；



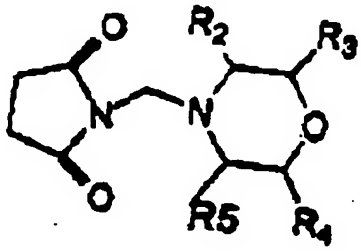
(VII)

结构式中：R_2、R_3、R_4、R_5表示$C_1\sim C_3$的短链正烷基或异烷基或氢原子；

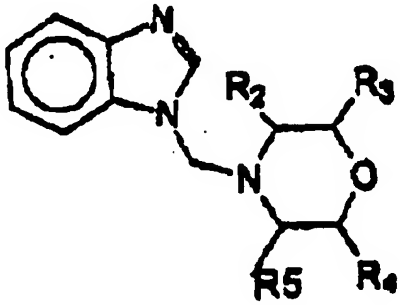
（G）化学结构式（IV）化合物和化学结构式（VIII）或（IX）化合物的酮交换反应；



(IV)



(VIII)



(IX)

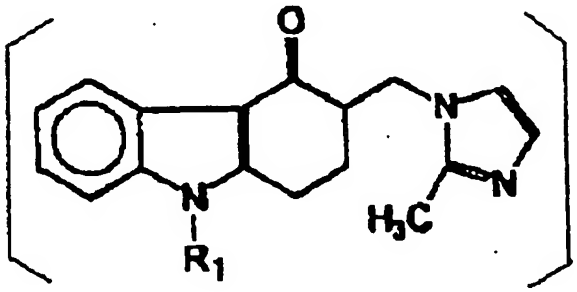
结构式中：R_1表示$C_1\sim C_6$的直链或脂环烷基，R_2、R_3、R_4、R_5表示$C_1\sim C_3$的短链正烷基或异烷基或氢原子.

4. 根据权利要求1至3之一的制备思丹西酮的众多重要中间体中，特别有用的化合物是1,1,2,2,3-五氢-9-甲基-3-〔(2′-甲基咪唑基-1)-甲基〕-4-氧代咔唑和二氧化硅或离子交换树脂的复合物.

说 明 书

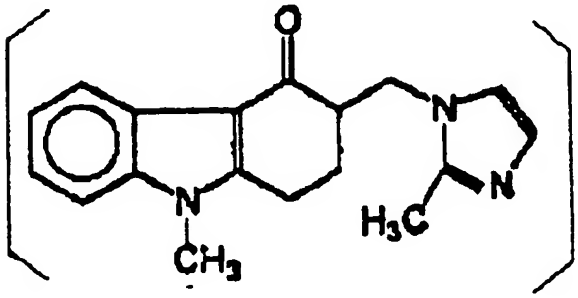
恩丹西酮及其生理盐的合成

本发明涉及医药用的一种有机碱及其合格的生理盐和溶剂化物的制备，该种化合物的化学结构通式用式（Ⅰ）表示：



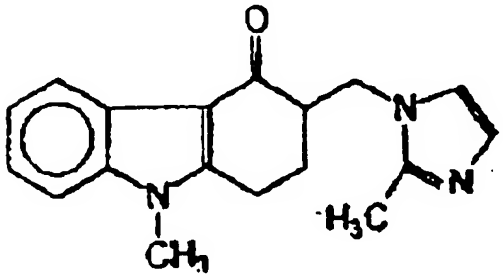
A·S (I)

结构式中：A表示盐酸、硫酸、氢溴酸、草酸、马来酸、无机酸或有机酸；S表示水溶剂；R_1表示$C_1 \sim C_6$的直链或脂环状烷基．在医药上它的盐酸盐二水化合物（X）习惯商品名为盐酸恩丹西酮．



$HCl \cdot 2H_2O$ (X)

化学名为1,1,2,2,3-五氢-9-甲基-3-〔（2′-甲基咪唑-1-基）-甲基〕-4-氧代-咔唑．结构式用（Ⅱ）表示：



(II)

根据本发明制备的该有机碱及其合格的生理盐和溶剂化物作为选择性5—羟基色胺（5-HT_3）受体的拮抗剂是强有效的．现在称为5-HT_3受体包括称为5-HT_3，5-HT_3M'或5-HT_3 'M－式' 受体，过去对这类受体已有较详细的描述．例如在下述若干论文中：Fozard, et al Eur. J.pharmacol., 1979.59,195～210; Irelard, Straughan, Typers,Brit.J.pharmacol., 1982,75 16p; Humphrey, Neuropharm 1984, 23, 1503～1570; Richardson et al, Nature 1985, 316, 126～131; Bradlay et al, Neuropharm 1986,25,563～576．已发现许多化合物是5-HT_3受体的有效拮抗剂，它们通常是氮杂双环衍生物，苯甲酸衍生物或咪唑衍生物，在下列专利中揭示了这些化合物的化学结构式；它们是美国专利：2100259 2125398 2131420 2132189 2145416 2152049 2153821和2169292．欧洲专利：111608 116255 158265 191562 210840 — 214772 219103 221702 226267 227215 230718 235878 242973 225545 220011 275669．澳大利亚专利：8767121．德国公开专利：3740352．日本公开特许：昭61-212521，昭62-77380，昭62-77381．中国专利申请号85105643．

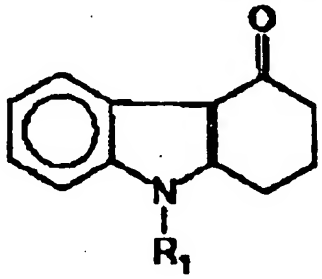
本项研究旨在发明批量生产恩丹西酮及其合格生理盐的新方法，提供有实用价值和经济效益的生产工艺．

按照本专利提供的制备通式（Ⅰ）化合物的第一种方法（A），通式为（Ⅱ）的化合物或含量大于30％的混合物被选择性

地作用于弱酸性离子交换树脂或硅酸G（≤100目）或卡普隆粉或硅藻土或阳性氧化铝载体上和合适浓度的无机酸或有机酸溶液，在固一液界面上发生反应，高选择性地得到通式（Ⅰ）化合物。

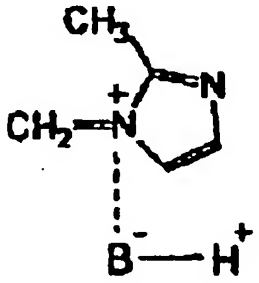
按照本专利提供的制备通式（Ⅰ）化合物的第二种方法（B），通式为（Ⅱ）的化合物或含量大于30%的混合物连续地加入到水一醇溶剂中，同时连续地通入氯化氢等气体，可经连续地获得通式为（Ⅰ）的化合物。

按照本专利提供的制备通式（Ⅱ）的制备方法（E），化学结构式（Ⅳ）化合物是芳香酮类化合物，2-甲基咪唑是芳香胺类化合物，它们在普通的Mannich反应条件下，主要发生胺醛的缩合反应，生成树脂状缩聚物，而且，属芳香酮类的通式（Ⅳ）化合物的

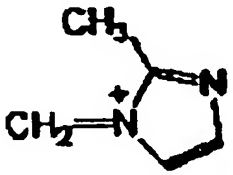


(Ⅳ)

3位氢酸性不够强，但在Lewis酸类催化剂作用下，通过Lewis酸负离子中心电荷向醛胺缩合的亚胺正离子的部份转移，例如经可能的中间体结构式（Ⅺ），促进了亚胺正离子中间体（Ⅻ）的生成，化学结构式（Ⅳ）的烯醇式中间体化合物（ⅩⅢ）与亚胺中间体（Ⅻ）的加成完成通式（Ⅱ）

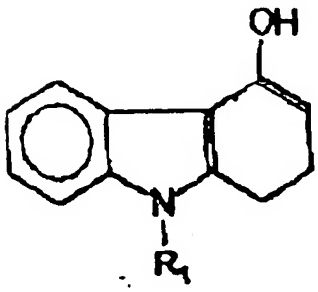


(Ⅺ)



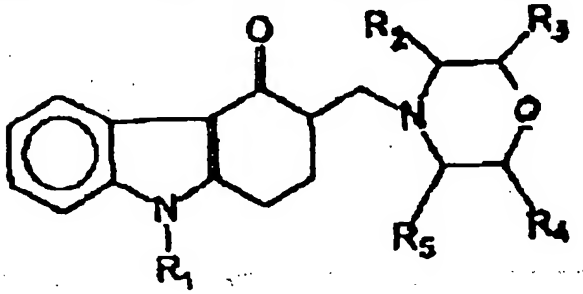
(Ⅻ)

化合物的制备，在结构式（XIII）中R_1表示$C_1 \sim C_6$的直链或脂环状烷基.

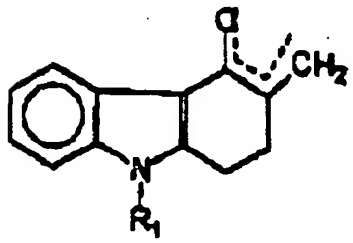


(XIII)

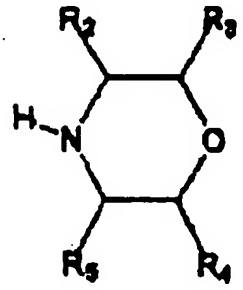
按照本专利提供制备通式（II）化合物的制备方法（C），在含水的质子型混合溶剂中，化学结构式（III）化合物在Lewis酸催化下迅速解离成可能结构式为（XIV）的不稳定中间体和化学结构式为（VII）的杂环胺分子，化学结构式中：R_1表示$C_1 \sim C_6$的直链或脂环状烷基；R_2、R_3、R_4、R_5表示$C_1 \sim C_3$的短链正烷基或异烷基.



(III)



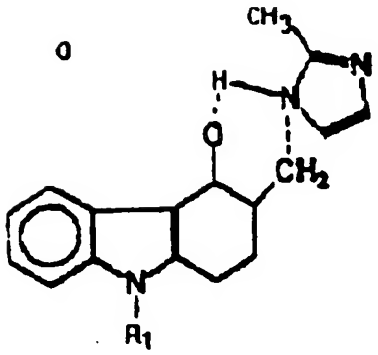
(XIV)



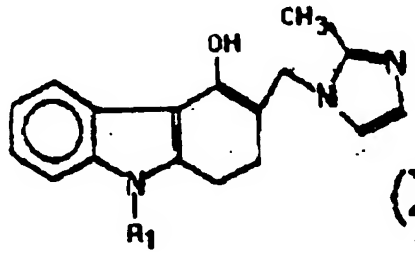
(VII)

中间体（XIV）经2-甲基咪唑的1，4加成中间过渡态（XVI），首先生成化学结构式（XVII）的化合物，（XVII）的C_3，C_4间的双键处于顺式位置，因此，立即转化成能量上较稳定的反式位置，也即（XVII）的酮式结构，该酮式结构就是结构式为

（Ⅱ）的化合物.

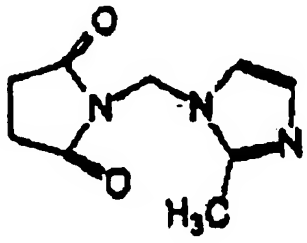


(XVI)

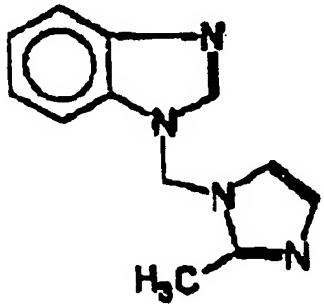


(XVII)

按照本专利提供的制备化学结构式（Ⅱ）的制备方法（D），在酸性的质子型溶剂中化学结构式（Ⅳ）化合物和化学结构式（Ⅴ）或（Ⅵ）的化合物在加温条件下（如25－100℃）发生

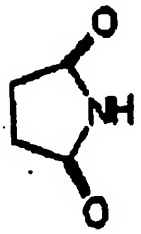


(V)

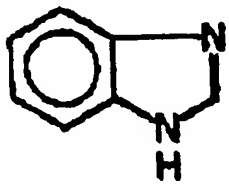


(VI)

酮交换反应，反应结束后，可以分离得到琥珀酰亚胺（XVIII）或苯骈咪唑（XIX），所以，该交换反应的第一步极可能是



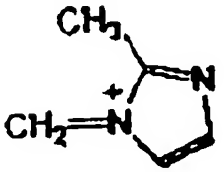
(XVIII)

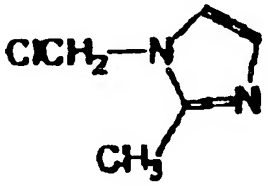


(XIX)

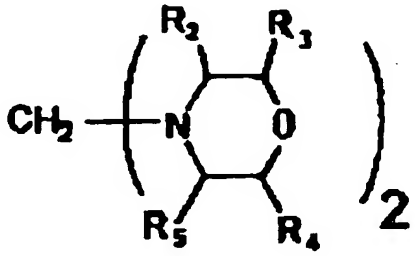
（Ⅴ）或（Ⅵ）发生质子诱导的分解反应，除生成（XVIII）或（XIX）外，还生成重要的亚胺正离子中间体（XII）和（Ⅳ）立即发生加成反应而生成化学结构式（Ⅱ）的化合物．在实施制备方法（D）时，反应中间体不需要分离纯化，即是一锅法合成．在制备

方法（D）中需要的（V）或（VI）从易得的N-氯甲基-2-甲基咪唑（XX）分别和琥珀亚胺或苯骈咪唑加热反应而得.

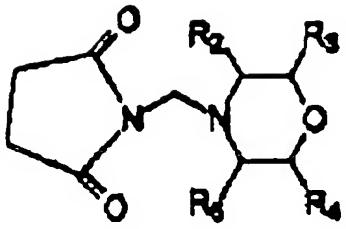

(XII)


(XX)

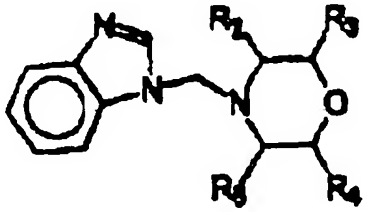
按照本专利提供的制备化学结构式（III）化合物的制备方法（F），吡唑-4-酮（IV），多聚甲醛和结构式（VII）化合物的催化缩合反应，为加快反应，反应中用如$AgNO_3$，$Cu_2X_2(X=Cl,Br,I)$，$Cu(OAc)_2$，Al_2O_3等固体Lewis酸催化剂或它们的混合型复合催化剂或盐酸等无机酸，实施制备方法（F）时，可以是三种组份同时加入，也可以先不加入（IV）和酸，让多聚甲醛和结构式（VII）的胺类化合物，先发生醛胺缩合反应，该缩合反应只可能生成醛胺分子比例为1：2的缩合物（XXI），（XXI）同样可和（IV）在酸性条件下反应生成结构式（III）化合物.


(XXI)

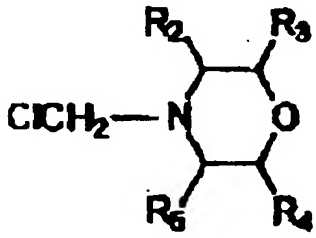
按照本专利提供的制备结构式（III）化合物的制备方法（G），化学结构式（IV）化合物和化学结构式（VIII）或（IX）化合物的酮反应，交换反应最好在加温条件下进行（例如30～150℃），而制备方法（G）中所用的化学结构式（VIII）或（IX）化合物分别由化学结构式化合物（XXII）与琥珀酰亚胺（XVIII）或苯骈咪唑（XIX）加热反应而得.



(VIII)

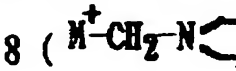


(XI)



(XXII)

结构式中：R_2、R_3、R_4、R_5表示$C_1 \sim C_3$的短链正烷基或异烷基或氢原子.

按照本专利制备的恩丹西酮及众多的中间体中，特别要提到1,1,2,2,3－五氢-9－甲基-3-〔（吗啡啉基-N）-甲基〕-4-氧代咔唑，1,1,2,2,3-五氢-9-甲基-3-〔（2′,6′-二甲基-吗啡啉基-N）-甲基〕-4-氧代咔唑，上述二种咔唑的化学结构由^1HNMR、IR、MS、$^{13}CNMR$和元素分析结果确认.$-CH_2CH_2CH-$的化学位移在1.80～3.00 ppm,9位$N-CH_3$的特征性单峰化学位移在3.68 ppm，3位的次甲基桥氢在^1HNMR谱上发现出二个双峰，在谱图上还出现吗啡啉部的特征性谱图，在质谱图上，除出现预计的分子离子峰外，M/Z198（  ）是上述二种咔唑的共同基峰. 在IR谱图上，除羰基的1640cm^{-1}峰外，还普遍有1580，1480cm^{-1}的苯环峰. 1,1,2,2,3-五氢-9-甲基-3-〔（2′-甲基咪唑-1）甲基〕-4-氧代咔唑及它与硅胶复合物的结构差别证明在红外光谱上，复合物的苯环基的特征吸收光谱分别位移30～40cm^{-1}说明该复合物是层迭的平板

状结构，该咔唑是作为负电荷中心，不饱和键与氧化硅的空穴间形成氢键，保证了酸和溶剂分子从另一面向咔唑分子的进攻.

本专利涉及到经过新颖反应中间体化合物合成恩丹西酮及其合洛生理盐的新方法，反映中间体是经光谱技术和元素分析确认结构的新化合物，具有原料易得，反应条件温和，操作简便，产物易于提纯的优点.

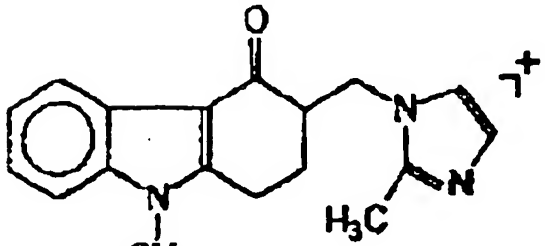
下面的例子说明本发明在经已知化合物校正过的毛细管测定熔点，红外、氢核磁谱和质谱分别在Simadzu IR-440型、Bruker AM 300型和HP 5989A型光谱仪上测定.

实例A_1:

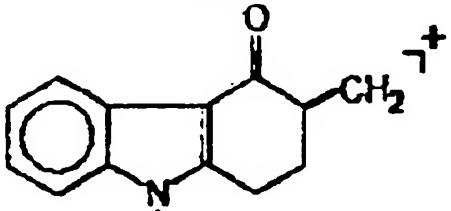
盐酸1,1,2,2,3-五氢-9-甲基-3〔(2′-甲基咪唑-1-基)甲基〕-4-氧代咔唑二水化合物（X）及一水化合物.

由5g（0.017mol）实例C，D或E制备的化合物（II）和50ml乙酸乙酯混合加热，使成小颗粒的悬浮液，趁热加入装有薄层层析硅胶柱中，柱直径5cm，柱长15cm，通入少量N_2气压力，先用300ml乙酸乙酯洗脱，收集之洗脱液蒸去乙酸乙酯，残留100mg黄色粘液，薄板层析检测为前沿杂质，继而用200ml乙酸乙酯洗脱收集液浓缩，残留物为白色固体，检测为实例F，G制备化合物（III），即回收原料0.8g，然后用1N HCl水溶液洗脱，继而用1000ml水洗脱，水溶液合并浓缩，冷却，结晶，抽滤，结晶物在红外上干燥，得4.75g标题化合物（X），产率90.54%，mp. 176~178℃，分析样品，用水重结晶一次，并在具有P_2O_5干燥器中真空干燥，得到一水化合物，元素分析：$C_{18}H_{19}N_3O\cdot HCl\cdot H_2O$，MW，347.83，实测值（计算值）%：C 62.44（62.16），H 6.12（6.38），N 12.12

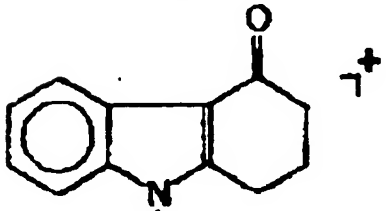
(12.08), Cl 10.46 (10.19); IR: υ_{max} 3200-3400 (OH), 1630 (C=C), 1620 (C=O), 1580, 1480, 760cm^{-1}, MS: M/Z,



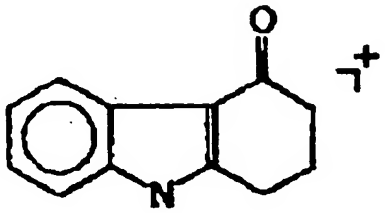
293 ( ),



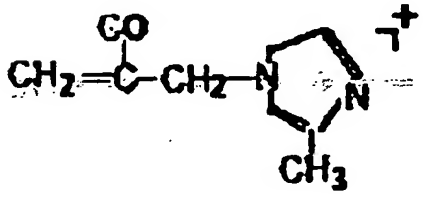
211 ( ),



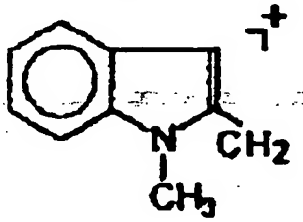
198 ( ), 183 (



),



149 ( ),



143 ( ),

55 (H_2C-CHC$\equiv$O$^+$); ^1HNMR:$DMSO-d_6$, δ_{1H}, 1.90~2.25, 2.96~3.25, (5H, m, $-CH_2-CH_2-CH-$), 2.65 (3H, S, $C-CH_3$), 3.74 (3H, S, $N-CH_3$), 4.23~4.31, 4.63~4.69 (2H, dd-dd, $-CH_2-$), 7.55~7.69 (2H, d, d CH=CH), 7.19~7.29, 7.50~7.55 (3H, m, ArH), 7.97~8.05 (1H, m, ArH); $^{13}CNMR$:δ_{13C}, 191.18, 152.83, 144.44, 137.41, 124.05, 122.65, 122.26, 122.20, 122.01, 117.71, 110.60, 110.26, 46.87, 45.36, 29.76, 26.20, 20.64, 10.42.

实例A_2:

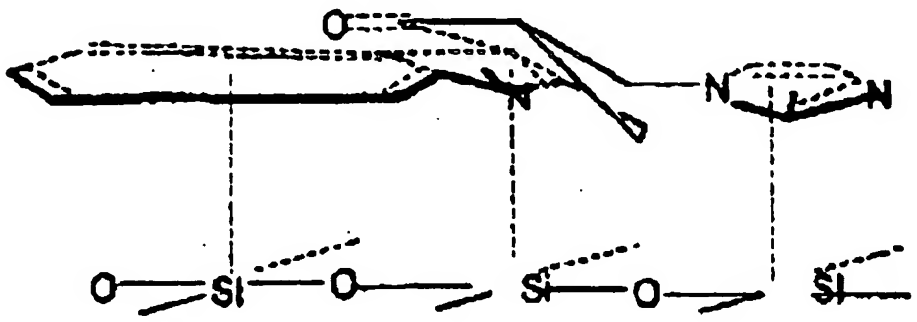
盐酸1,1,2,2,3-五氢-9-甲基-3-〔(2′-甲基咪唑-1-基)甲基〕-4-氧代咔唑二水化合物(X)及一水化合物.

由5g(0.017mol)实例C,D或E制备的化合物(Ⅱ)悬浮于40ml乙醇中,加入30g氢型阳离子交换树脂,搅拌半小时后,悬浮物消失,继续搅拌半小时,滤出树脂,并用乙醇洗涤,抽干树脂,放回到烧杯中,加入40ml 0.1N HCl,搅拌1~2小时,滤出酸液,树脂中再加入新鲜40ml 0.1N HCl搅拌,如此反复操作多次,滤出酸液合并,浓缩,冷却,结晶,滤出,干燥,得4.5g标题化合物(X),产率72.05%,mp. 176~178℃,放入具P_2O_5干燥器中真空干燥,得一水化合物,元素分析:$C_{18}H_{19}N_3O\cdot HCl\cdot H_2O$,MW,374.83,实测值(计算值)%:C 62.46(62.16),H 6.24(6.12),N 12.04(12.07),Cl 10.41(10.19);IR、MS、^1HNMR、$^{13}CNMR$光谱与实例A_1产物相同.

实例A_3:

10mg1,1,2,2,3-五氢-9-甲基-3〔(2′-甲基咪唑-1-基)甲基〕-4-氧代咔唑溶解于5ml乙酸乙脂中在薄层硅胶板上作薄板层析,用5~10%乙酸乙脂—正已烷作梯次展开剂,手提式紫外灯检测试剂的展开状况,用双光束反射式NICOLET IR光谱仪,测定红外光谱,发现原归属为C=C的吸收峰从1630cm^{-1}位移到1675cm^{-1}处,而原归属为C=O吸收峰仅从1620cm^{-1}位移到1625cm^{-1}处,表明该氧代咔唑在硅胶上呈重叠式吸附,分子间氢键由C=C双键作电子结体和硅胶的空穴作电子受体而形成,而C_4位的C=O键则不与吲哚环和咪唑环在同一平面上,故C=O键的位移值极小,1,1,2,2,3-五氢-9-甲基

-3-〔（2′-甲基咪唑-1- 基）甲基〕-4-氧代咔唑在SiO_2表面上呈如下结构:



HYPETCHEM 三型量化计算表明分子的π体系取共平面，羰基位于平面外，二个甲基也位于平面外的构型，分子可获得3.214千焦耳/摩尔的稳定能，而从双键的红外位移值计算（$E=h\upsilon$）分子π电子和SiO_2空穴间的作用能为0.5382千焦耳/摩尔.

实例B:

盐酸1,1,2,2,3-五氢-9-甲基-3-〔（2′-甲基咪唑-1-基）甲基〕-4-氧代咔唑二水化合物（X）

实例C，D或E制备的化合物（Ⅱ），用甲醇重结晶2次，干燥后，取0.25g（0.85mmol）（Ⅱ）溶于5ml乙醇中，通入干HCl气体，待pH3时，停止，冷却，结晶，过滤出固体，用水重结晶，得220mg白色标题化合物（X），产率70.45%，mp. 176~178℃，IR、MS、^1HNMR、$^{13}CNMR$光谱与实例A_1产物相同.

实例C:

1,1,2,2,3-五氢-9-甲基-3-〔（2′-甲基咪唑-1-基）甲基〕-4-氧代咔唑（Ⅱ）

实例C_1:

2.5g 2-甲基咪唑溶于20ml乙醇中，在水浴中冷却，加入等当量的浓H_2SO_4搅拌，除去冰浴，加入2.98g（10mmol）实例F或G制备的化合物（III），90℃左右，搅拌5小时，蒸去大部分乙醇溶剂，冷却，加入100ml水，析出固体，抽滤，滤并用水洗涤，干燥，得2.5g标题化合物（II），mp. 220~223℃，含量85%，分析样品：用甲醇重结晶，干燥，得2.2g白色粉状物，mp. 227~228℃，产率75.1%，元素分析：$C_{18}H_{19}N_3O$，MW，293.35，实测值（计算值）%：C 73.45（73.70），H 6.54（6.53），N 14.01（14.32）；IR、MS测定结果与实例C_2相同；^1HNMR：$CDCl_3$，δ_{1H} 1.80~1.94，2.04~2.25，2.82~3.02（5H，m，$-CH_2-CH_2CH-$），2.46（3H，S，$C-CH_3$），3.68（3H，S，NCH_3），4.07~4.14，4.62~4.69（2H，dd-dd，$-CH_2-$），6.91~6.95（2H，d-d，CH=CH），7.31~7.33（3H，m，ArH），8.22~8.26（1H，m，ArH）。

实例C_2:

在250ml三口瓶中，加入3克（0.01mol）1,1,2,2,3-五氢-9-甲基-3〔（吗啡啉基-N-）甲基〕-4-氧代咔唑，用3N盐酸调节至pH6，然后，加入40ml正丙醇及5克（0.06mol）2-甲基咪唑，搅拌至反应物溶解，在95℃下加热35小时，冷却，滤出固体，在甲醇中脱色和重结晶，得到2.62克白色粉末状固体，mp. 227~228℃，产率85.9%，元素分析$C_{18}H_{19}N_3O$，MW，293.35，实验值（计算值）%：C 73.45（73.72），H 6.54（6.58），N 14.01（14.22）；IR：υ_{max} 3050，2920，2850，1630，1620，1580，1480，1280，

1200. 760cm^{-1}; MS: M/Z 293 (M^+), 211, 198, 183, 149, 144, 55; $\delta_{1H}(CDCl_3)$ 8.23~8.26 (1H, m, ArH), 7.33~7.31 (3H, m, ArH), 6.95~6.91 (2H, dd, CH=CH), 4.69~4.62, 4.14~4.07 (2H, dd, dd, $-CH_2-$), 3.68 (3H, S, NCH_3), 2.46 (3H, S, $C-CH_3$), 3.02~2.82, 2.25~2.04, 1.94~1.80 (5H, m, $-CH_2-CH_2CH-$) ppm.

实例C_3:

实验步骤类似于实例C_2，不同之处仅在于加料次序，游离和卟唑曼尼希碱和2-甲基咪唑先溶解于正丙醇中，再用3N盐酸调节反应混合物至pH6，在95℃下加热35小时后，按实例C_2方法纯化产物，胺交换产率达81.3%.

实例C_4:

在250ml三口瓶中加入7.1克（0.06mol）2-甲基咪唑盐酸盐，3克（0.01mol）1,1,2,2,3-五氢-9-甲基-3-〔（吗啡啉基-N-）甲基〕-4-氧代卟唑和40ml正丙醇，用3N盐酸调节反应混合物至pH6，在95℃下加热35小时，随后按例实C_2方法作后处理，得到2.35克标题化合物，产率77.01%.

实例D_1:

1,1,2,2,3-五氢-9-甲基-3-〔（2′-甲基咪唑-1-基）甲基-4-氧代卟唑（II）.

14.85g（0.15mol）琥珀酰亚胺和15ml二甲基甲酰胺溶液滴

加入由13克（0.1mol）N-氯甲基-2-甲基咪唑，10.6克（0.1mol）碳酸钠和50ml二甲基甲酰胺组成的反应混合物中，滴加时保持反应温度为60℃，滴加完后，慢慢升温至100℃，保持此温度搅拌2小时，冷却，倾入到1000ml冰水中，有机相用苯提取3×15ml，提取液和有机相合并，水洗至中性，蒸去溶剂，得到粗产品15.9克，产率92%，产物不经纯化就用于下一步反应。

2.0g（10mol）化合物（IV），2.0g（10.4mmol）N-（2′-甲基咪唑-1-基）甲基—琥珀酰亚胺溶于25ml乙醇中，用2N HCl调节pH6，加热回流，搅拌10小时，冷却，加入100ml 1N HCl，滤出固体不溶物，水相用苯提取，苯层水洗，分出水，用无水硫酸钠干燥，并蒸去苯回收化合物（IV）0.8g，水相碱化用Na_2CO_3，析出固体，抽滤，滤并水洗，干燥，得标题化合物1.2g mp. 220～223℃，产率68.26%。

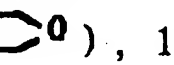
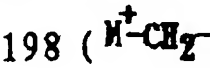
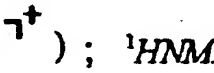
实例E:

1,1,2,2,3-五氢-9-甲基-3-［（2′-甲基咪唑-1-基）甲基］-4-氧代咔唑（II）

2.0g（10mmol）化合物（IV），1.2g（40mmol）多聚甲醛，1.6g（19.5mmol）2-甲基咪唑及40ml乙醇搅拌混合，再加入Cu_2Cl_2-HCl催化剂，加热回流，搅拌20小时，冷却，50ml 1N HCl搅拌，不溶物滤出，水相用苯提取3×3ml，苯层合并，用水洗，然后用无水硫酸钠碱化，析出固体，冷却，抽滤，滤出固体水洗，干燥，得0.85g粗产物，mp. 218～222℃用甲醇重结晶，干燥，得0.26g克产物，产率8.87%，mp. 228～229℃，IR、MS、^1HNMR同于实例C制备化合物。

实例F:

1,1,2,2,3-五氢-9-甲基-3-〔(吗啡啉-N-基)甲基〕-4-氧代咔唑(Ⅱ)

2.0g(10mmol)化合物(Ⅳ),1.2g(40mmol)多聚甲醛,1.74g(20mmol)吗啡啉溶于20ml乙酸中,搅拌,加热70℃下反应5小时,冷却,加入50ml 1N HCl,搅拌,滤出不溶物,水相用苯提取3×3ml,苯层合并,用水洗涤,苯层用无水硫酸钠干燥,蒸去苯,残留物0.2g,为回收的(Ⅳ)。水相与洗涤水合并,用固体*NaOH*碱化,析出固体,冷却,抽滤,滤并用水洗,干燥,得2.2g标题化合物(Ⅱ),产率81.21%,分析样品:用乙酸乙酯重结晶,得白色晶体,mp. 165.5~166.5℃,元素分析:$C_{18}H_{22}N_2O_2$,MW,298.37,实测值(计算值)%:C 71.94 (72.46),H 7.53(7.43),N 9.28(9.38);IR:$\upsilon_{C=O}$ 1640,1620,1580,1480,760cm^{-1};MS:M/Z,299(M^++1),298(M^+),211(),198(),183,100();^1HNMR:$CDCl_3$,δ_{1H},8.23(1H,m,ArH),7.26~7.30(3H,m,ArH),3.70~3.78(4H,m,CH_2OCH_2),3.86(3H,S,$N-CH_3$),2.20~3.06(11H,m,CH_2NCH_2,CH_2CH_2CH,CH_2)。

实例G:

1,1,2,2,3-五氢-9-甲基-3-〔(吗啡啉-N-基)甲基〕-4-氧代咔唑(Ⅲ)

14.85g(0.15mol)琥珀酰亚胺和15ml二甲基甲酰胺溶液滴加入由13克(0.1mol)N-氯甲基-2-甲基咪唑10.6克(0.1mol)碳酸

钠和50ml二甲基甲酰胺组成的反应混合物中，滴加时保持反应温度为60℃，滴加完后，慢慢升温至100℃，保持此温度搅拌2小时，冷却，倾入到1000ml冰水中，有机相用苯提取3×15ml，提取液和有机相合并，水洗至中性，蒸去溶剂，得到粗产品15.9克，产率92%，产物不经纯化就用于下一步反应。

2.0g（10mmol）化合物（IV），2.0gN-（吗啡啉-N-基）甲基-琥珀酰亚胺溶于乙醇中，用2N HCl调节pH6，加热回流20小时，蒸去乙醇，加入50ml 1N HCl，搅拌溶解，滤出不溶物，滤液用苯提取，苯层合并，用水洗，无水硫酸钠干燥，蒸去苯，残留物显黄色固体，0.5g检测为回收的化合物（IV），水相用*NaOH*碱化，析出固体，过滤，滤并水洗，干燥，得1.2g标题化合物，产率53.69%，分析样品用乙酸乙酯重结晶，mp. 165.5~166.5℃，IR、MS、^{1}*HNMR*光谱数据同实例F制得化合物一致。

[19] Patent Office of the People's Republic of China [11] Disclosure No. CN 1113234A

[12] Disclosure Statement of Invention Patent Application

[21] Application no. 94114311.2

[51] Int. Cl[6]
C07D233/54

[43] Disclosure date: December 13, 1995

[22] Filing date: 12-29-94

[71] Applicant: Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences
Address: 354 Fenglin Road, Shanghai, 200032
Co-applicant: Changzhou Pharmaceutical Factory No. 3
[72] Inventors: Wu Guosheng, Zhou Wenjuan, Chen Guoping, Jin Xiongmin, Qian Shuqin, Chen Rongqing, Wang Shufen

[74] Patent agency: Jiangsu Province Patent Agency
Agents: Xu Dongtao, Shao Yuanling

Number of pages in description:
Number of pages in attached drawings:

[54] Title of invention: Synthesis of Ondansetron and Its Normal Saline

[57] Abstract

The present invention relates to a method of preparing the chemical compound with chemical structural formula (I) and its corresponding free alkali (II).

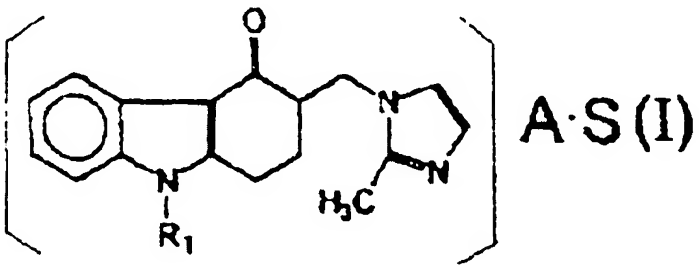
In the structural formula, A represents hydrochloric acid, sulfuric acid, hydrobromic acid, oxalic acid, maleic acid, and perchloric acid, which can be mixed with (II) to produce acceptable normal saline non-organic and organic acids; S represents the water solvent.

The chemical name of the chemical compound (I) is the normal saline solvate of 1, 1, 2, 2, 3-pentahydro-9-methyl-3-[(2-methyl-imidazole-1-base) methyl]-4-oxocarbazole. It is an effective 5-HT_3 and receptor antagonist. Clinically, it is highly effective against nausea and vomiting resulting from cisplatin and non-cisplatin chemotherapy and radiation therapy.

(BJ) No. 1456

Claims

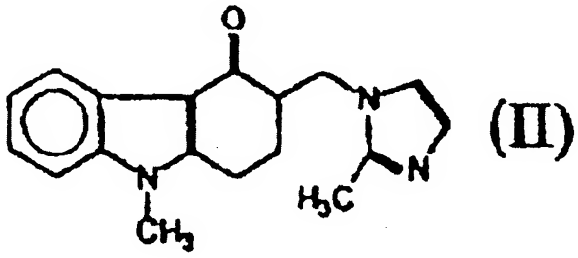
1. The method of preparing general formula (I):



In the structural formula: A represents hydrochloric acid, sulfuric acid, hydrobromic acid, oxalic acid, maleic acid, organic acid(s), and inorganic acid(s); S represents the water solvent. R_1 represents C_1~C_6 straight chains or alicyclic alkyls.

The method of preparing general formula (I) including:

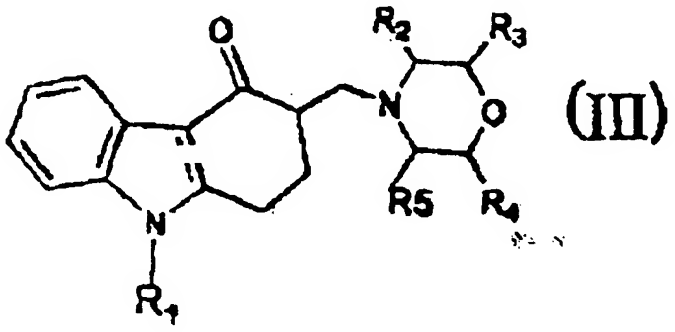
(A) Chemical compound(s) or other protected derivatives of general formula (II), or the solid-liquid interface salt-formation reactions between reaction mixtures containing more than 30% [formula II??] and A;



(B) Chemical compound(s) or other protected derivatives of general formula (II), or the liquid-gas interface salt-formation reactions between reaction mixtures containing more than 30% [formula II??] and A;

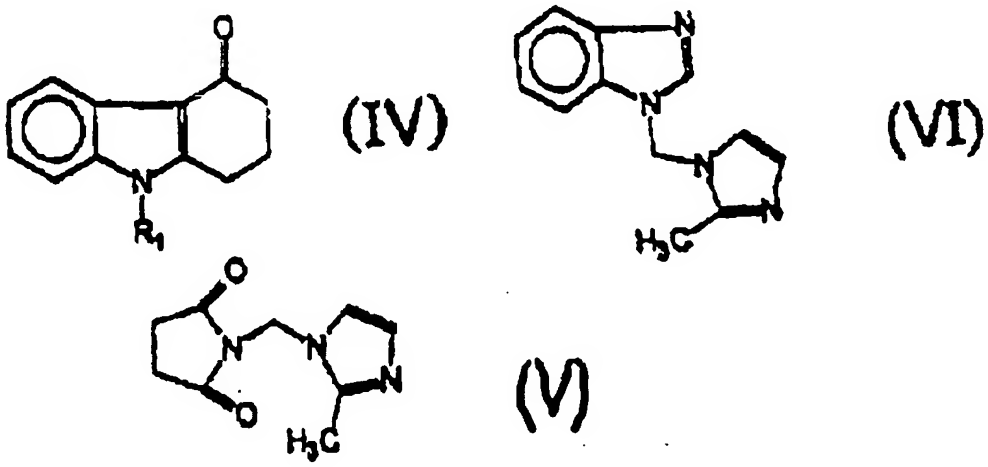
2. The method, according to claim 1, of preparing general formula (II):

(C) The exchange reaction(s) between the chemical compound in general formula (III) and 2-methyl imidazole or other amines.



In the structural formula: R_1 represents C_1~C_6 straight chains or alicyclic alkyls. R_2, R_3, R_4, R_5 represent C_1~C_3 short chain normal alkyls or isoalkyls or hydrogen atoms. R_2, R_3, R_4, R_5 may be the same or different substitution groups, or there may be no substitution group.

(D) The ketone exchange reaction(s) between the compound with chemical structural formula (IV) and the compound with chemical structural formula (V) or (VI);

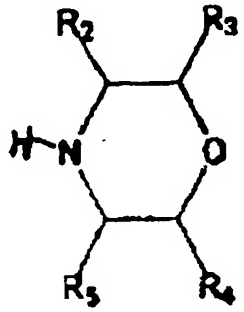


In the structural formulas: R_1 represents C_1~C_6 straight chains or alicyclic alkyls;

(E) Catalytic condensation reactions of the chemical compound with chemical structural formula (IV), paraformaldehyde, and 2-methyl imidazole. The solid catalysts used in the reactions are $AgNO_3$, Cu_2X_2 (X = Cl, Br, I), $Cu(OAc)_2$, Al_2O_3 Lewis acid or a composite catalyst made of a mixture of these.

3. The method, according to claim 2, of preparing chemical structural formula (III), which includes:

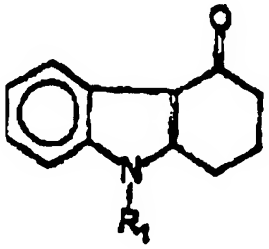
(F) Catalytic condensation reactions between the chemical compound with chemical structural formula (IV), paraformaldehyde, and the chemical compound with structural formula (VII). The solid catalysts used in the reactions are $AgNO_3$, Cu_2X_2 (X = Cl, Br, I), $Cu(OAc)_2$, Al_2O_3 Lewis acid or a composite catalyst made of a mixture of these, or hydrochloric acid, sulfuric acid, inorganic acid(s);



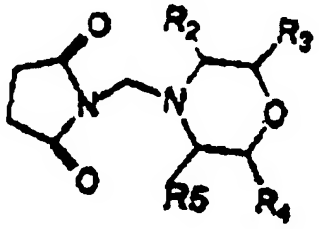
(VII)

In the structural formula: R_2, R_3, R_4, R_5 represent C_1~C_3 short chain normal alkyls or isoalkyls or hydrogen atoms;

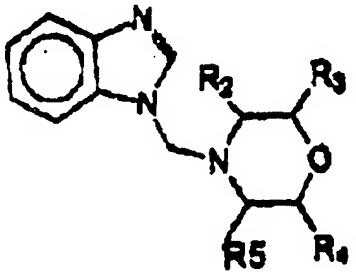
(G) Ketone exchange reactions of the chemical compound with chemical structural formula (IV) and chemical compounds with chemical structural formulas (VIII) or (IX);



(IV)



(VIII)



(IX)

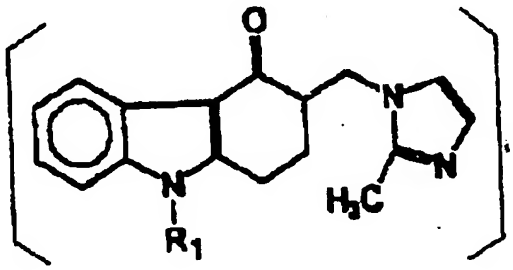
In the structural formulas: R_1 represents C_1~C_6 straight chains or alicyclic alkyls, and R_2, R_3, R_4, R_5 represent C_1~C_3 short chain normal alkyls or isoalkyls or hydrogen atoms.

4. Many important intermediate forms of the ondansetron prepared according to one of patent claims 1 through 3, with especially useful chemical compounds being composites of 1,1,2,2,3-pentahydro-9-methyl-3-[(2'-methyl imidazole-1)-methyl]-4-oxocarbazole and silicon dioxide or ion exchange resin(s).

Description

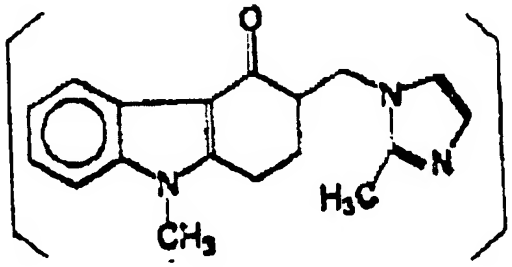
Synthesis of Ondansetron and Its Normal Saline

The present invention relates to the preparation of an organic base for pharmacological use and its suitable normal saline and solvent compound(s). The chemical structural formula (I) for this type of compound is represented as:



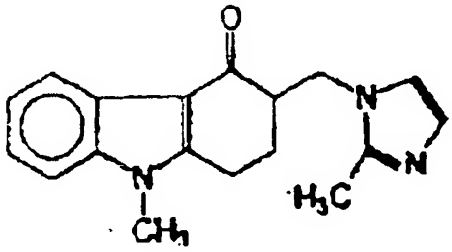
A·S (I)

In the structural formula: A represents hydrochloric acid, sulfuric acid, hydrobromic acid, oxalic acid, maleic acid, inorganic acid(s), or organic acid(s); S represents the water solvent. R_1 represents C_1~C_6 straight chains or alicyclic alkyls. In pharmacology the customary commercial name of its hydrochloride dihydrate compound (X) is ondansetron hydrochloride.



HCl·2H$_2$O (X)

The chemical name is 1,1,2,2,3-pentahydro-9-methyl-3-[(2'-methyl imidazole-1-base)-methyl]-4-oxocarbazole. The structural formula is represented in (II):



(II)

[formula (II)]

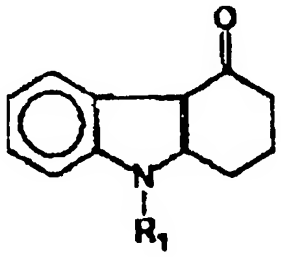
The organic base and its acceptable normal saline and solvent compound prepared according to the present invention serve as selective 5-hydroxytryptamine (5-HT_3) receptor antagonists and are highly effective. What are now called 5-HT_3 receptors include 5-HT_3, 5-HT_3M', or 5-HT_3 "M-type" receptors. In the past, the description of this category of receptors was more detailed. Examples of this appear in the following literature: Fozard, et al., Eur. J. pharmacol., 1979.59, 195~210; Irelard, Straughan, Typers, Brit. J. pharmacol., 1982, 75 16p; Humphrey, Neuropharm 1984, 23, 1503~1570; Richardson et al., Nature 1985, 316, 126~131; Bradlay et al., Neuropharm 1986, 25, 563~576. It has been discovered that many chemical compounds are effective antagonists of 5-HT_3 receptors. Typically, they are azabicyclic derivatives, benzoic acid derivatives, or imidazole derivatives. The chemical structural formulas for these compounds are presented in the following patents; US patents: 2100259, 2125398, 2131420, 2132189, 2145416, 2152049, 2153821, and 2169292. European patents: 111608, 116255, 158265, 191562, 210840, 214772, 219103, 221702, 226267, 227215, 230718, 235878, 242973, 225545, 220011, 275669. Australian patent: 8767121. German laid-open patent: 3740352. Japanese unexamined patent publication 1985-212521, 1986-77380, 1986-77381. Chinese patent application number 85105643.

The aim of this study was to invent a new method of mass producing ondansetron and its normal saline, providing a production process with practical value and economic benefits.

The first method (A) of preparing the compound with general formula (I) provided according to the present patent, wherein the chemical compound with general formula (II)or a mixture with content greater than 30% is selectively applied to a weakly-acidic ion exchange resin or hydrated silica G (<100 mesh), or Capuron powder or diatomite, or a cationic aluminum oxide carrier, and an appropriate concentration of inorganic acid or organic acid solvent. A reaction occurs at the solid-liquid interface, yielding the chemical compound with general formula (I) in a highly selective manner.

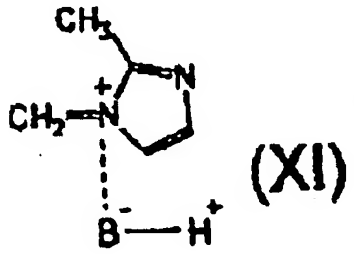
The second method (B) of preparing the compound with general formula (I) provided according to the present patent, wherein the chemical compound with general formula (II) or a mixture with a content of greater than 30% is continuously added to a water-alcohol solvent, while at the same time passing through chlorinated hydrogen and other gases, making it possible to obtain the chemical compound of general formula (I) in a continuous manner.

According to method (B) of preparing general formula (II) provided in the present patent, the chemical compound with chemical structural formula (IV) is an aromatic ketone, and 2-methyl imidazole is an aromatic amine chemical compound. Under the conditions of a regular Mannich reaction, they mainly undergo amine-aldehyde condensation reactions, forming polycondensate in resin form. Moreover, the three-position hydracidity of the aromatic ketone chemical compound with general formula

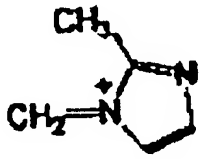


(IV)

(IV) is not sufficiently strong, but under the effect of Lewis acid catalysts, the partial shift of negative ion central electrical charges towards the positive imine ions of the aldehyde amine condensation, as in the possible intermediate structure (XI), promotes the formation of positive ion imine intermediate form (XII). The addition of the intermediate enol form with chemical structural formula (IV) and intermediate imine (XII) completes the preparation of the chemical compound with general formula (II).

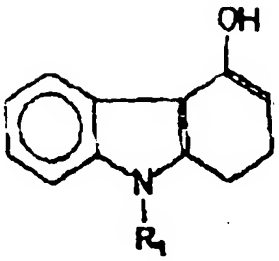


(XI)



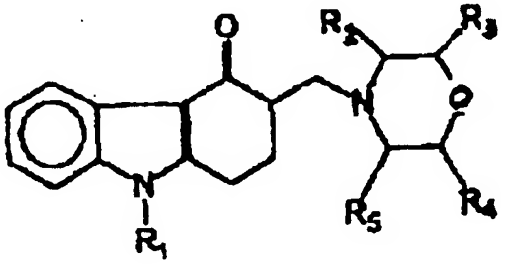
(XII)

In structural formula (XIII), R_1 represents C_1~C_6 straight chains or alicyclic alkyls.

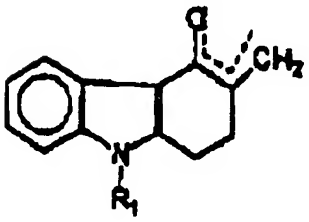


(XIII)

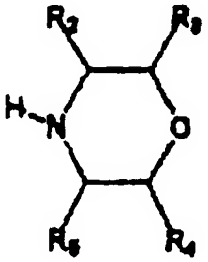
Method (C) of preparing the compound with general formula (II) provided in the present patent, wherein the chemical compound with chemical structural formula (III) when mixed in a proton-like solvent containing water rapidly ionizes under the effects of Lewis acid catalysis, forming the unstable intermediate form with possible structural formula (XIV) and heterocyclic amine molecules with structural formula (VII). In the structural formula, : R_1 represents C_1~C_6 straight chains or alicyclic alkyls; R_2, R_3, R_4, R_5 represent C_1~C_3 short chain normal alkyls or isoalkyls.



(III)

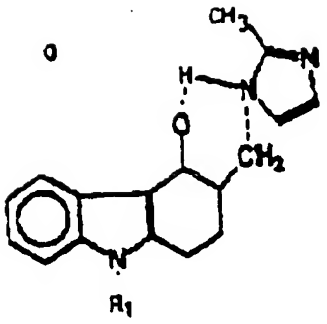


(XIV)

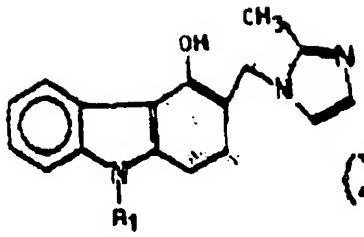


(VII)

Intermediate form (XIV) undergoes a transitional phase (XVI) between the 1 and 4 additions of 2-methyl imidazole, first forming the chemical compound with chemical structural formula (XVII). The double chains between C_3 and C_4 are in the cis-form position, and thus, they immediately switch to energetically more stable trans-form positions, which is the ketone form structure of (XVII). This ketone form structure is the chemical compound with structural formula (II).

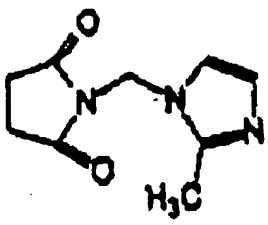


(XVI)

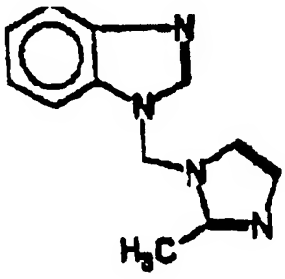


(XVII)

Method (D) of preparing chemical structural formula (II) provided in the present patent, wherein a ketone exchange reaction occurs between the chemical compound with chemical structural formula (IV) in an acidic protonic solvents and chemical compounds with chemical structural formulas (V) or (VI) under conditions of heating (such as 25~100°C).

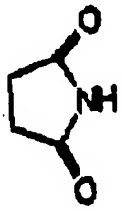


(V)

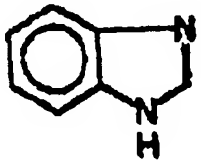


(VI)

Once the reaction is completed, succinimide (XVIII) or benzimidazole (XIX) may be separated out. Therefore, it is very possible that the first step of this exchange reaction is

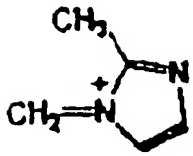


(XVIII)

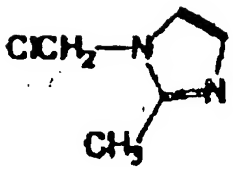


(XIX)

that (V) or (VI) undergoes proton induction decomposition reaction(s), and in addition to forming (XVIII) or (XIX) also forms the important imine positive ion intermediate forms (XII) and (IV), which immediately undergo addition reactions to form the chemical compound with chemical structural formula (II). When implementing preparation method (D), it is not necessary to separate and purify the intermediate forms from the reactions, and synthesis can be accomplished using a one-vessel method.
The (V) or (VI) needed for preparation method (D) are obtained through separate heating reactions between readily available N-chloromethyl-2-methyl imidazole (XX) and succinimide [? character appears to be missing] or benzimidazole.

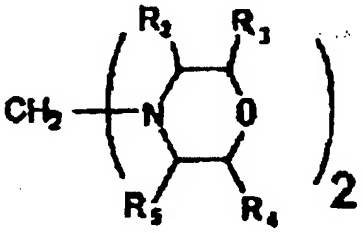


(XII)



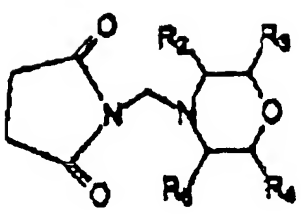
(XX)

Method (F) of preparing the chemical compound with chemical structural formula (III) provided in the present patent, wherein catalytic condensation reactions take place among carbazole-4-ketone (IV), paraformaldehyde, and the chemical compound with structural formula (VII). In order to accelerate the reaction, solid Lewis acid catalysts such as $AgNO_3$, Cu_2X_2 (X = Cl, Br, I), $Cu(OAc)_2$, Al_2O_3, etc. or composite catalysts made from a mixture of these, or inorganic acids such as hydrochloric acid are used in the reaction. When implementing preparation method (F), the three types of components may be added simultaneously, and it is also possible to not add (IV) and the acid at first, allowing the paraformaldehyde and the amine compound with structural formula (VII) to first undergo an aldehyde-amine condensation reaction. This condensation reaction can only form condensate (XXI) with a 1:2 aldehyde to amine molecular ratio. (XXI) can similarly react with (IV) under acidic conditions to form the chemical compound with structural formula (III).

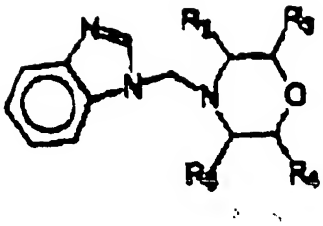


(XXI)

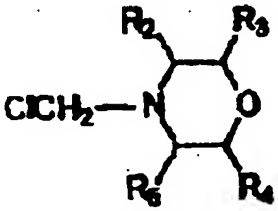
Method (G) of preparing the chemical compound with structural formula (III) provided in the present patent, wherein the chemical compound with chemical structural formula (IV) and the chemical compound with chemical structural formula (VIII) or (IX) undergo a ketone reaction. The exchange reaction is best performed under conditions of heating (such as 30~150°C). The chemical compounds with structural formulas (VIII) or (IX) used in preparation method (G) are obtained through separate heating reactions between the compound with chemical structural formula (XXII) and succinimide (XVIII) or benzimidazole (XIX).



(VIII)

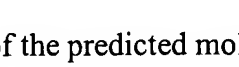


(XI)



(XXII)

In the structural formulas: R_2, R_3, R_4, R_5 represent C_1~C_3 short chain normal alkyls or isoalkyls or hydrogen atoms.

Among the ondansetron and the many intermediate forms prepared according to the present patent, particular mention is made of 1,1,2,2,3-pentahydro-9-methyl-3-[morpholine-N)-methyl]-4-oxocarbazole, 1,1,2,2,3-pentahydro-9-methyl-3-[(2',6'-dimethyl-morpholine-N)-methyl]-4-oxocarbazole. The chemical structures of the two types of carbazoles described above have been confirmed by the results of ^1HNMR, IR, MS, $^{13}CNMR$, and elemental analysis. The chemical displacement of $-CH_2CH_2CH-$ is 1.80~3.00 ppm. The characteristic single peak chemical displacement of 9-position N-CH_3 is at 3.68 ppm. Two double peaks are discovered in the ^1HNMR spectrum for 3-position methylidyne bridge hydrogen. Characteristic spectrograms for the morpholine section also appear in the spectrograms. In the mass spectrograms, in addition to the appearance of the predicted molecular ion peaks, M/Z198 ()is the common base peak for the two carbazoles mentioned above. In the IR spectrogram, in addition to the 1640 cm^{-1} peak of the carbonyl, 1580 and 1480 cm^{-1} benzene ring peaks were also prevalent. The structural differences between 1,1,2,2,3-pentahydro-9-methyl-3-[(2'-methyl imidazole-1) methyl]-4-oxocarbazole and its silica gel composite are proved in the infrared spectrum. The separate displacement of the characteristic absorption spectrum of the composite's benzene ring bases 30~40 cm^{-1} shows that this composite is a layered, flat structure.

The carbazole acts as a negative electrical charge center, and the holes between the unsaturated chains and the silicon oxide form hydrogen chains, ensuring that the acid and solvent molecules attack the carbazole molecule from another side.

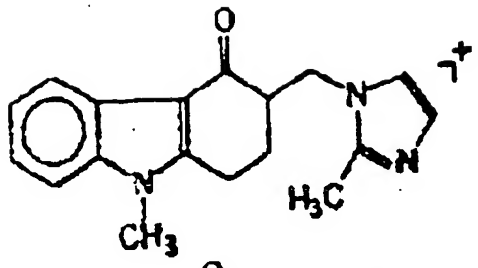
The present invention relates to a new method of synthesizing ondansetron and its acceptable normal saline through novel intermediate reaction compounds. The reflected intermediate forms are new compounds, the structures of which have been confirmed using spectrographic technology and elemental analysis. They possess the advantages of easily-obtainable raw materials, moderate reaction conditions, simple procedures, and products that are easily purified.

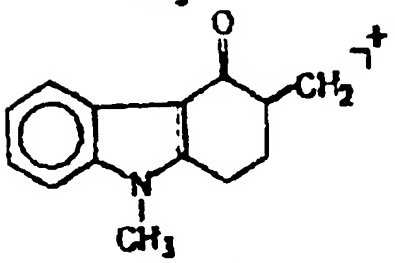
The following embodiments show that the melting point, infrared, hydrogen nucleus magnetic spectrum and mass spectrum of the present invention were measured in capillary tubes corrected using known compounds. The measurements were made using Simadzu model IR-400, Bruker model AM 300, and HP model 5989A spectrographs.

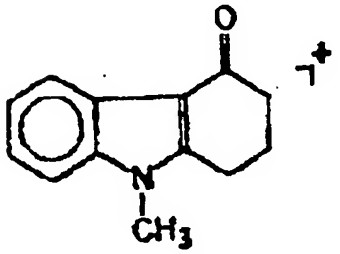
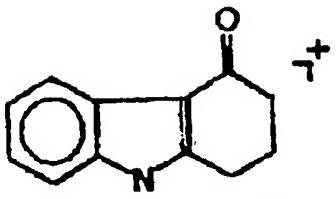
Embodiment A_1:

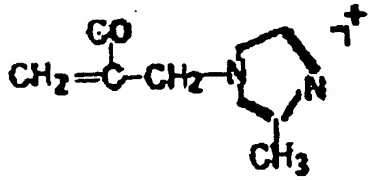
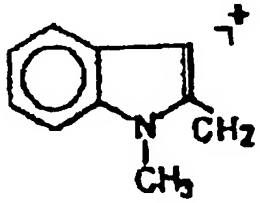
Hydrochloric acid 1,1,2,23-pentahydro-9-methyl-3[(2'-methyl imidazole-1-base)methyl]-4-oxocarbazole dihydrate chemical compound (X) and monohydrate chemical compound.

5 g (0.017 mol) of chemical compound (II) prepared in embodiments C, D, or E was mixed with 50 ml of ethyl acetate and heated, causing a suspension with small granules to form. While still hot, this was placed in a column layered with thin layers of silica gel. The diameter of the column was 5 cm, column length 15 cm. A small amount of N_2 gas was introduced. First, 300 ml ethyl acetate was used for elution, and the ethyl acetate was evaporated off from the collected eluent. 100 mg of yellow, viscous liquid remained, which, upon inspection of the layers was shown to be leading edge impurities. Next, 200 ml ethyl acetate was used for elution, and the collected liquid was concentrated. A white solid remains, which was shown upon inspection to be chemical compound (III) prepared in embodiments F, and G. 0.8 g of raw material was recovered. Next, an aqueous solution of 1 N HCl was used for elution, followed by elution with 1000 ml of water. The aqueous solutions were combined and concentrated, chilled, crystallized, and filtered. The crystallized material was dried in infrared [light?], yielding 4.75 g of title compound (X). The production rate was 90.54%, m.p. 176~178°. In the analysis of the sample, water was used for recrystallization once, and then vacuum drying was performed in a P_2O_5 dryer, yielding a monohydrate chemical compound. The elemental analysis is: $C_{18}H_{19}N_3O \cdot HCl \cdot H_2O$, MW, 347.83. Actual measured values (calculated values)%: C 62.44 (62.16), H 6.12 (6.38), N 12.12 (12.08), Cl 10.46 (10.19); IR $\upsilon_{[illegible]}$ 3200-3400 (OH), 1630 (C=C), 1620 (C=O), 1580, 1480, 760 cm^{-1}, MS: M/Z

293 (),

211 (),

198 (), 183 (),

149 (), 143 (),

55 (); ^{1}*HNMR:DMSO-d*$_6$, δ_{1H}, 1.90~2.25, 2.96~3.25, (5H, m, -CH_2-CH_2-CH-), 2.65 (3H, S, C-CH_3), 3.74 (3H, S, N-CH_3), 4.23-4.31, 4.63-4.69 (2H, dd-dd, -CH_2-), 7.55-7.69 (2H, d, d CH=CH), 7.19~7.29, 7.50~7.55 (3H, m, ArH), 7.97-8.05 (1H, m, ArH); ^{13}*CNMR*:δ_{13C}, 191.18, 152.83, 144.44, 137.41, 124.05, 122.65, 122.26, 122.20, 122.01, 117.71, 110.60, 110.26, 46.87, 45.36, 29.76, 26.20, 20.64, 10.42.

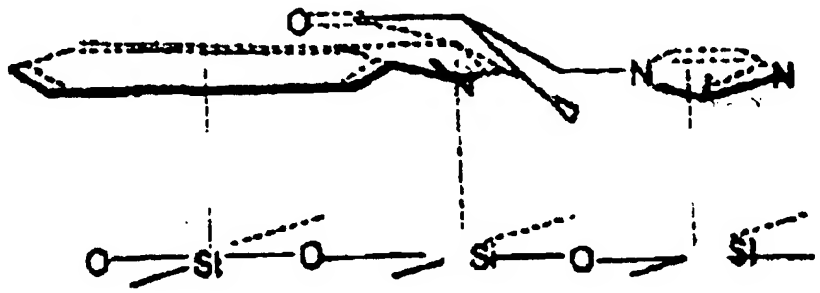
Embodiment A_2:

Hydrochloric acid 1,1,2,2,3-pentahydro-9-methyl-3-[(2'-methyl imidazole-1-base)methyl]-4-oxocarbazole dihydrate chemical compound (X) and monohydrate chemical compound.

5 g (0.017 mol) of chemical compound (II) prepared in embodiment C, D, or E was suspended in 40 ml of ethyl alcohol. 30 g hydrogen-like cationic exchange resin was added. After agitating for half an hour, the suspended materials disappeared, and agitation continued for another half hour. The resin was filtered out and rinsed with ethyl alcohol. The resin was dried, and returned to the beaker. 40 ml of 0.1 N HCl was added, and it was agitated for 1~2 hours. The acid was filtered out, and 40 ml of fresh 0.1 N HCl was added to the resin. This procedure was repeated several times. The filtered acids were combined, concentrated, chilled, crystallized, filtered, and dried, yielding 4.5 grams of the title compound (X). The production rate was 72.05%, m.p. 176~178°C. The compound was placed in a dryer containing P_2O_5 for vacuum drying, yielding a monohydrate chemical compound. The elemental analysis was: $C_{18}H_{19}N_3O \cdot HCl \cdot H_2O$. MW, 374.83. Actual measured values (calculated values) %: C 62.46 (62.16), H 6.24 (6.12), N 12.04 (12.07), Cl 10.41 (10.19); IR, MS, ^{1}*HNMR*, ^{13}*CNMR* spectra were the same as the product in embodiment A_1.

Embodiment A_3:

10 mg 1,1,2,2,3-pentahydro-9-methyl-3- [(2'-methyl imidazole-1-base)methyl]-4-oxocarbazole dissolved in 5 ml ethyl acetate was thinly layered on a thin plate of silica gel. 5~10% ethyl acetate-normal hexane was used as the graded developer, and a hand-held ultraviolet lamp was used to inspect the development of the reagents. The infrared spectrum was measured using a double beam reflecting Nicolet IR spectrograph, and it was discovered that the original C=C absorption peak had been shifted from 1630 cm^{-1} to 1675 cm^{-1}. The C=O absorption peak was only shifted from 1620 cm^{-1} to 1625 cm^{-1}, showing that on the silica gel this oxocarbazole exhibited overlapping adsorption. The intermolecular hydrogen chains are formed by the C=C double chains serving as electron donors, while the holes in the silica gel serve as electron acceptors. The C=O chain of the C_4 position is not in the same plane as the indole ring and the carbazole ring. Due to the extremely small displacement value of the C=O chain, 1,1,2,2,3-pentahydro-9-methyl-3-[(2'-methyl imidazole-1-base)methyl]-4-oxocarbazole exhibited the following structure on the SiO_2 surface:



HYPETCHEM 3-type quantization calculations showed that the molecule's π systems are coplanar. The carbonyl group is located outside the plane, and the two methyl groups are also in a configuration outside the plane. The molecule yields 3.214 kilojoules/mole of

stable energy. Moreover, based on the double chain infrared displacement value calculation ($E=h\nu$), the effect of the molecule's π electrons and the holes in the SiO_2 can be 0.5382 kilojoule/mole.

Embodiment B:

Hydrochloric acid 1,1,2,2,3-pentahydro-9-methyl-3-[(2'-methyl imidazole-1-base)methyl]-4-oxocarbazole dihydrate chemical compound (X)

Chemical compound (II) prepared in embodiment C, D, or E was recrystallized twice using methyl alcohol. After drying, 0.25 g (0.85 mmol) of (II) was dissolved in 5 ml of ethyl alcohol. HCl gas was passed through it until the pH reached 3, then the procedure was stopped. This was followed by chilling, crystallization, and filtering of the solid, which was recrystallized using water, yielding 220 mg of white title compound (X), for a yield of 70.45%, m.p. 176~178°C. the IR, MS, ^{1}*HNMR*, and ^{13}*CNMR* spectra were the same as for the product in embodiment A_1.

Embodiment C:

1,1,2,2,3-pentahydro-9-methyl-3-[(2'-methyl imidazole-1-base)methyl]-4-oxocarbazole (II)

Embodiment C_1:

2.5 g 2-methyl imidazole was dissolved in 20 ml ethyl alcohol and chilled in a water bath. An equivalent amount of concentrated H_2SO_4 was added and agitated. The ice bath was removed, and 2.98 g (10 mmol) of chemical compound (III) from embodiments F or G was added. At approximately 90°C it was agitated for 5 hours. Most of the ethyl alcohol solvent was evaporated off, and [the remaining substance] was chilled. 100 ml water was added, and the solid was separated out and filtered, rinsing with water during filtration. Drying yielded 2.5 g of the title compound (II), m.p. 220~223°C, content 85%. Sample analysis: methyl alcohol was used for recrystallization, which, after drying, yielded 2.2 g white powdery material, m.p. 227~228°C, production rate 75.1%. Elemental analysis: $C_{18}H_{19}N_3O$, MW, 293.35. Actual measured values (calculated values) %: C 73.45 (73.70), H 6.54 (6.53), N 14.01 (14.32); IR, MS measurement results are the same as for embodiment C_2. ^{1}*HNMR*: *CDCl*$_3$, δ_{1H} 1.80~1.94, 2.04~2.25, 2.82~3.02 (5H, m, -CH_2-CH_2CH-), 2.46 (3H, S, C-CH_3), 3.68 (3H, S, NCH_3) 4.07~4.14, 4.62~4.69, (2H, dd-dd, -CH_2-), 6.91~6.95 (2H, d-d, CH=CH), 7.31~7.33 (3H, m, ArH), 8.22~8.26 (1H, m, ArH).

Embodiment C_2:

3 grams (0.01 mol) 1,1,2,2,3-pentahydro-9-methyl-3[(morpholine-N-)methyl]-4-oxocarbazole was placed in a 250 ml three-mouthed flask, and 3N hydrochloric acid was used to adjust the pH to 6. Next, 40 ml *n*-propyl alcohol and 5 grams (0.06 mol) 2-methyl imidazole were added, and agitated until the reactants dissolve. This was heated at 95°C for 35 hours, chilled, and the solids filtered. It was then decolored in methyl alcohol and recrystallized, yielding 2.62 grams of white powdery solid, m.p. 227~228°C, for a yield of 85.9%. The elemental analysis was $C_{18}H_{19}N_3O$, MW, 293.35. Experimental values (calculated values) %: C 73.45 (73.72, H 6.54 (6.58), N 14.01 (14.22); IR: $\nu_{[illegible]}$ 3050, 2920, 2850, 1630, 1620, 1580, 1480, 1280, 1200. 760 cm^{-1}; MS: M/Z 293 (M^+), 211, 198, 183, 149, 144, 55; δ_{1H} (*CDCl*$_3$) 8.23~8.26 (1H, m, ArH), 7.33~7.31 (3H, m, ArH),

6.95~6.91 (2H, dd, CH=CH), 4.69~4.62, 4.14~4.07 (2H, dd, dd, $-CH_2-$), 3.68 (3H, S, NCH_3), 2.46 (3H, S, $C-CH_3$), 3.02~2.82, 2.25~2.04, 1.94~1.80 (5H, m, $-CH_2-CH_2CH-$) ppm.

Embodiment C_3:

The experimental procedure was similar to that of embodiment C_2, with the only difference being the order in which the ingredients were added. Free and carbazole Mannich base and 2-methyl imidazole were first dissolved in *n*-propyl alcohol. Next, 3N hydrochloric acid was used to adjust the reaction mixture to pH6. After heating at 95°C for 35 hours, the product was purified according to the method in embodiment C_2. The amine exchange production rate was 81.3%.

Embodiment C_4:

7.1 grams (0.06 mol) 2-methyl imidazole hydrochloride, 3 grams (0.01 mol) 1,1,2,2,3-pentahydro-9-methyl-3-[(morpholine-N-)methyl]-4-oxocarbazole, and 40 ml *n*-propyl alcohol were placed in a 250 ml three-mouthed beaker. 3N hydrochloric acid was used to adjust the reaction mixture to pH6. This was heated at 95°C for 35 hours, and then handled according to the method in embodiment C_2, yielding 2.35 grams of the title compound, for a yield of 77.01%.

Embodiment D_1:

1,1,2,2,3-pentahydro-9-methyl-3-[(2'-methyl imidazole-1-base)methyl]-4-oxocarbazole (II).

14.85 g (0.15 mol) succinimide and 15 ml dimethyl formamide solution was added in dropwise to a reaction mixture composed of 13 grams (0.1 mol) N-chloromethyl -2-methyl imidazole, 10.6 grams (0.1 mol) sodium carbonate, and 50 ml dimethyl formamide. During the addition by drops, a reaction temperature of 60°C was maintained. Once addition by drops was completed, the temperature was slowly raised to 100°C, and this temperature was maintained for 2 hours of agitation. [The mixture] was chilled and decanted into 1000 ml of ice water. Benzene was used to extract 3 × 15 ml of the organic phase. [??] The extracted liquid was combined with the organic phase and rinsed with water until neutral. The solvent was evaporated off, yielding 15.9 grams of unrefined product, for a yield of 92%. The product was used for the next reaction without undergoing purification.

2.0 g (10 mol) of chemical compound (IV), 2.0 g (10.4 mmol) N-(2'-methyl imidazole-1-base)methyl-succinimide was dissolved in 25 ml ethyl alcohol. 2N HCl was used to adjust the pH to 6. [The solution] was heated at reflux, agitated for 10 hours and then chilled. 100 ml of 1N HCl was added and the undissolved solids were filtered out. Benzene was used to extract the aqueous phase, and the benzene layers were rinsed with water. The water was separated out, and anhydrous sodium sulfate was used for drying. The benzene was evaporated off to recover 0.8 g of chemical compound (IV). Na_2CO_3 was used to alkalinize the aqueous phase. The solids were separated out, filtered, rinsing with water during filtration. [The solids] were dried, yielding 1.2 g of the title compound, m.p. 220~223°C, for a yield of 68.26%.

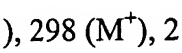
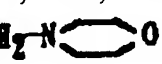
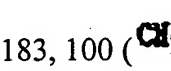
Embodiment E:

1,1,2,2,3-pentahydro-9-methyl-3-[(2'-methyl imidazole-1-base)methyl]-4-oxocarbazole (II)

2.0 g (10 mmol) of chemical compound (IV), 1.2 g (40 mmol) paraformaldehyde, 1.6 g (19.5 mmol) 2-methyl imidazole and 40 ml ethyl alcohol were agitated and mixed. Next, Cu_2Cl_2-HCl catalyst was added, and heated at reflux, and agitated for 20 hours. [The mixture was then] chilled, and agitated with 50 ml 1N HCl. The undissolved material was filtered out. Benzene was used to extract 3 × 3 ml of the aqueous phase. The benzene layers were combined and rinsed with water. Anhydrous sodium sulfate was then use for alkalinization, and the solids were separated out. [The solution was] chilled, and filtered, using water to rinse the filtered solids. Drying yielded 0.85 g of unrefined product, m.p. 218~222°C. Methyl alcohol was used for recrystallization, and drying yielded 0.26 grams of product. The production rate is 8.87%, m.p. 228~229°C. IR, MS ^{1}*HNMR* were the same as for the chemical compound prepared in embodiment C.

Embodiment F:

1,1,2,2,3-pentahydro-9-methyl-3-[(morpholine-N-base)methyl]-4-oxocarbazole (II)

2.0 g (10 mmol) of chemical compound (IV), 1.2 g (40 mmol) paraformaldehyde, and 1.74 g (20 mmol) morpholine were dissolved in 20 ml ethyl alcohol and agitated. [The mixture] was heated at 70°C to react for 5 hours and then chilled. 50 ml 1N HCl was added, agitated, and the undissolved material was filtered out. Benzene was used to extract 3 × 3 ml of the aqueous phase. The benzene layers were combined and rinsed with water. The benzene layers were dried using anhydrous sodium sulfate. The benzene was evaporated off, and the remaining 0.2 g of material was recovered [compound] (IV). The aqueous phase was combined with the rinse water, solid NaOH used for alkalinization, and the solids were separated out. [The solution] was chilled, filtered, rinsing with water during filtration, and dried, yielding 2.2 g of the title compound (II), for a yield of 81.21 %. Sample analysis: ethyl acetate was used for recrystallization, yielding white crystals, m.p. 165.5~166.5°C. Elemental analysis: $C_{18}H_{22}N_2O_2$, MW, 298.37. Actual measured values (calculated values) %: C 71.94 (72.46), H 7.53 (7.43), N 9.28 (9.38); IR: $\nu_{[illegible]}$ 1640, 1620, 1580, 1480, 760 cm^{-1}; MS: M/Z, 299 (M^++1), 298 (M^+), 211 (), 198 (), 183, 100 (); ^{1}*HNMR*: $CDCl_3$, δ_{1H}, 8.23 (1H, m, ArH), 7.26-7.30 (3H, m, ArH), 3.70~3.78 (4H, m, CH_2OCH_2), 3.86 (3H, S, N-CH_3), 2.20~3.06 (11H, m, CH_2NCH_2, CH_2CH_2CH,CH_2).

Embodiment G:

1,1,2,2,3-pentahydro-9-methyl-3-[(morpholine-N-base)methyl]-4-oxocarbazole (III)

14.85 g (0.15 mol) succinimide and 15 ml dimethyl formamide solution was added in drops to a reaction mixture composed of 13 grams (0.1 mol) N-chloromethyl-2-methyl imidazole, 10.6 grams (0.1 mol) sodium carbonate, and 50 ml dimethyl formamide. During the addition in drops a reaction temperature of 60°C was maintained. After the completion of the addition in drops, the temperature was slowly raised to 100°C, and this temperature was maintained for 2 hours of agitation. [The solution] was chilled and decanted into 1000 ml of ice water. Benzene was used to extract 3 × 15 ml of the organic phase. The extracted liquid was combined with the organic phase and rinsed with water until neutral. The solvent was evaporated off, yielding 15.9 grams of

unrefined product, for a yield of 92%. The product was used in the next reaction without purification.

2.0 g (10 mmol) of chemical compound (IV), 2.0 g N-(morpholine-N-base) methyl-succinimide was dissolved in ethyl alcohol. 2N HCl was used to adjust the pH to 6. This was heated at reflux for 20 hours. The ethyl alcohol was evaporated off, and 50 ml 1N HCl was added. [The solution] was agitated to dissolve [the solids], and the undissolved material was filtered out. Benzene extraction was used on the filtrate. The benzene layers were combined, rinsed with water, and dried with anhydrous sodium sulfate. The benzene was evaporated off. leaving a bright yellow solid. 0.5 g was found to be recovered chemical compound (IV). NaOH was used to alkalinize the aqueous phase. The solids were separated out. [The solution] was filtered, rinsing with water during filtration. Drying yielded 1.2 g of the title compound, for a yield of 53.69%. The analyzed sample was recrystallized using ethyl acetate, m.p. 165.5~166.5°C. IR, MS, $^{1}HNMR$ spectrum data was consistent with the chemical compound obtained in embodiment F.